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ORIGINAL RESEARCH

Mineralocorticoid Receptor Antagonists in Myocardial Infarction Patients

A Systematic Review and Meta-Analysis of Randomized Trials

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ABSTRACT

BACKGROUND It is unclear whether routine mineralocorticoid antagonist (MRA) use benefits all post-myocardial infarction (MI) patients.

OBJECTIVES This study aims to perform a systematic review and study-level meta-analysis of randomized controlled trials comparing MRA vs no MRA in post-MI participants.

METHODS Using the intention-to-treat population, we used a fixed effect model with Peto odds ratios (ORs). Key outcomes were death and new or worsening heart failure (HF). Results were presented comparing the post-MI HF trial vs post-MI non-HF trials.

RESULTS Eleven trials, including 18,111 post-MI participants (9,064 MRA, 9,047 no MRA), were included; one trial (n = 6,642) recruited HF patients. Participants randomized to MRA compared to no MRA had a lower risk of death (OR: 0.85 [95% CI: 0.76-0.95]; $I^2 = 0\%$) and new or worsening HF (OR: 0.83 [95% CI: 0.73-0.94]; $I^2 = 26.8\%$). In the post-MI HF trial, MRA participants experienced a mortality benefit with a numerically larger risk difference (RD) (478/3,319 vs 554/3,313; OR: 0.84 [95% CI: 0.73-0.96]; RD: -2.3% [95% CI: -3.9% to -0.6%]) than in post-MI non-HF trials (219/5,745 vs 249/5,734; OR: 0.87 [95% CI: 0.72-1.05]; RD -0.5% [95% CI: -1.2% to 0.2%]; interaction $P = 0.73$). In the post-MI HF trial, MRA allocation decreased new or worsening HF (345/3,319 vs 391/3,313; OR: 0.87 [95% CI: 0.74-1.01]; RD: -1.4% [95% CI: -2.8% to 0.1%]) like in the post-MI non-HF trials (126/5,251 vs 167/5,241; OR: 0.75 [95% CI: 0.58-0.94]; RD: -0.8% [95% CI: -1.3% to -0.2%]; interaction $P = 0.29$).

CONCLUSIONS In post-MI patients, MRAs decrease the risk of all-cause mortality and new or worsening HF regardless of HF status. Numerically smaller absolute risk reductions were observed in the post-MI non-HF trials compared to the post-MI HF trial. (JACC Heart Fail. 2025;13:102531) © 2025 by the American College of Cardiology Foundation.

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SHOUT
SHARE
IT

ABBREVIATIONS AND ACRONYMS

HF = heart failure

MI = myocardial infarction

MRA = mineralocorticoid receptor antagonist

NNH = number needed to harm

NNT = number needed to treat

PCI = percutaneous coronary intervention

RD = risk difference

Even with advances in percutaneous coronary interventions (PCIs) and medical therapy, post-myocardial infarction (MI) patients continue to experience significant morbidity and mortality.[1] Mineralocorticoid receptor antagonists (MRAs) have been shown to decrease mortality compared to placebo among patients with acute myocardial MI complicated by left ventricular dysfunction and heart failure (HF).[2] However, several trials have not shown the clinical benefit of aldosterone antagonism in post-MI patients without HF and as a routine agent for post-MI care.[3,4] Although informative, these trials were underpowered despite having broad composite endpoints. The CLEAR (2 × 2 factorial randomized controlled trial of colchicine vs placebo and spironolactone vs placebo in patients with MI) trial enrolled 7,062 patients between 2018 and 2022 with a median follow-up of 3 years. Although spironolactone did not reduce the incidence of death from cardiovascular causes or new or worsening HF (HR: 0.89 [95% CI: 0.73-1.08]; $P = 0.23$), it did reduce new or worsening HF (HR: 0.69 [95% CI: 0.49-0.96]).

As this was the largest trial of routine aldosterone blockade in post-MI patients, a review of the totality of the data for: 1) all post-MI patients; and 2) post-MI without HF at the index presentation is needed. Therefore, we performed an updated systematic review and meta-analysis of randomized controlled trials to understand better the effect of aldosterone blockade compared to no aldosterone blockade in post-MI patients on important cardiovascular outcomes.[5]

METHODS

We registered the present meta-analysis in the PROSPERO International Prospective Register of Systematic Reviews (CRD42024619391) and followed the PRISMA reporting guidelines for the writing of the paper.[6] All data used in this paper is publicly available. No ethics approval was required given the study design.

SEARCH STRATEGY, SELECTION CRITERIA, AND DATA-EXTRACTION. Our investigator group completed a systematic review of PubMed, Embase, and Cochrane Central Register of Controlled Trials from inception to April 30, 2024, restricting the search to the English language. We included all randomized trials that compared MRA to no MRA on a background of usual care in post-MI participants. Supplemental Table 1 shows our complete search strategy.

Trials were eligible if the treatment duration was 3 months or more and data on efficacy or safety outcomes was available. We did not include any unpublished studies. Three authors (M.D., Z.C., A.C.) independently screened abstracts and evaluated full-text papers for eligibility, with conflicts resolved by consensus discussion. For each included trial, 2 authors independently compiled descriptive and outcome data from the principal and subsidiary publications, with additional data collected directly from collaborating investigators.

OUTCOMES. The primary efficacy outcome was all-cause mortality. The secondary efficacy outcome was new or worsening HF. Other outcomes included cardiovascular mortality, recurrent MI, or life-threatening ventricular arrhythmia. We tabulated safety outcomes for hyperkalemia and new or worsening renal failure. We used the definitions of outcomes used by the original trials and their subsidiary publications. Trials for which outcome data was unavailable were excluded for that specific outcome.

RISK OF BIAS ASSESSMENT. The included trials' risk of bias was assessed using Cochrane's Collaboration Risk-of-Bias Tool 2.[7] Two authors (M.D. and Z.C.) independently evaluated the 5 domains of risk of bias.

STATISTICAL ANALYSIS. All analyses were performed using the intention-to-treat population, meaning all randomized participants were included in their initially allocated study group. We used a fixed effect model with Peto odds ratios (ORs) as our primary analysis to calculate pooled OR and 95% CI given a previous meta-analysis showed studies with rare events.[5] We presented our meta-analysis comparing the post-MI trial that randomized participants with HF (post-MI HF trial) vs trials who predominantly included all-comers or who did not include HF participants (post-MI non-HF trials). We

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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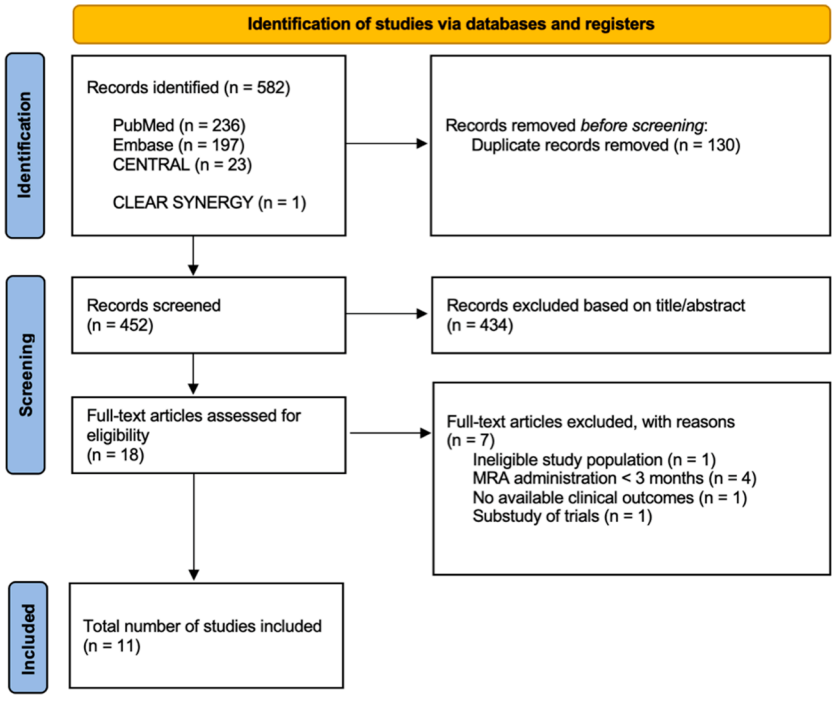
FIGURE 1 PRISMA Flowchart


Identification of studies via databases and registers
Identification
Records identified (n = 582)
PubMed (n = 236)
Embase (n = 197)
CENTRAL (n = 23)
CLEAR SYNERGY (n = 1)
Records removed *before screening*:
Duplicate records removed (n = 130)
Screening
Records screened
(n = 452)
Records excluded based on title/abstract
(n = 434)
Full-text articles assessed for eligibility
(n = 18)
Full-text articles excluded, with reasons
(n = 7)
Ineligible study population (n = 1)
MRA administration < 3 months (n = 4)
No available clinical outcomes (n = 1)
Substudy of trials (n = 1)
Included
Total number of studies included
(n = 11)

MRA = mineralocorticoid receptor antagonist.

used random effects using the restricted maximum likelihood estimator with the DerSimonian-Laird method as a sensitivity analysis. We also performed other sensitivity analyses using Peto OR, including only placebo-controlled trials for all-cause mortality and new or worsening HF. Using meta-regression, we explored sources of potential heterogeneity by using follow-up duration, PCI rates, and control group baseline risk as variables of interest for both primary and secondary efficacy outcomes. We derived absolute effects from the relative effects, assuming the Peto OR as a valid estimate of the true OR and using the no MRA arm as the baseline risk.[8] We then used the absolute risks to calculate the number needed to treat (NNT) and the number needed to harm (NNH).

We used the I^2 statistic to evaluate heterogeneity.[9] As per the Cochrane Collaboration, I^2 statistic thresholds were defined as 0% to 40% for low, 30% to 60% for moderate, 50% to 90% for substantial, and 75% to 100% for considerable. We assessed for publication bias using the funnel plot and Egger's test. All analyses were performed using the *metan* package with STATA version 18.0 (StataCorp). A value of $P < 0.05$ was considered statistically significant. We did not adjust for multiplicity.

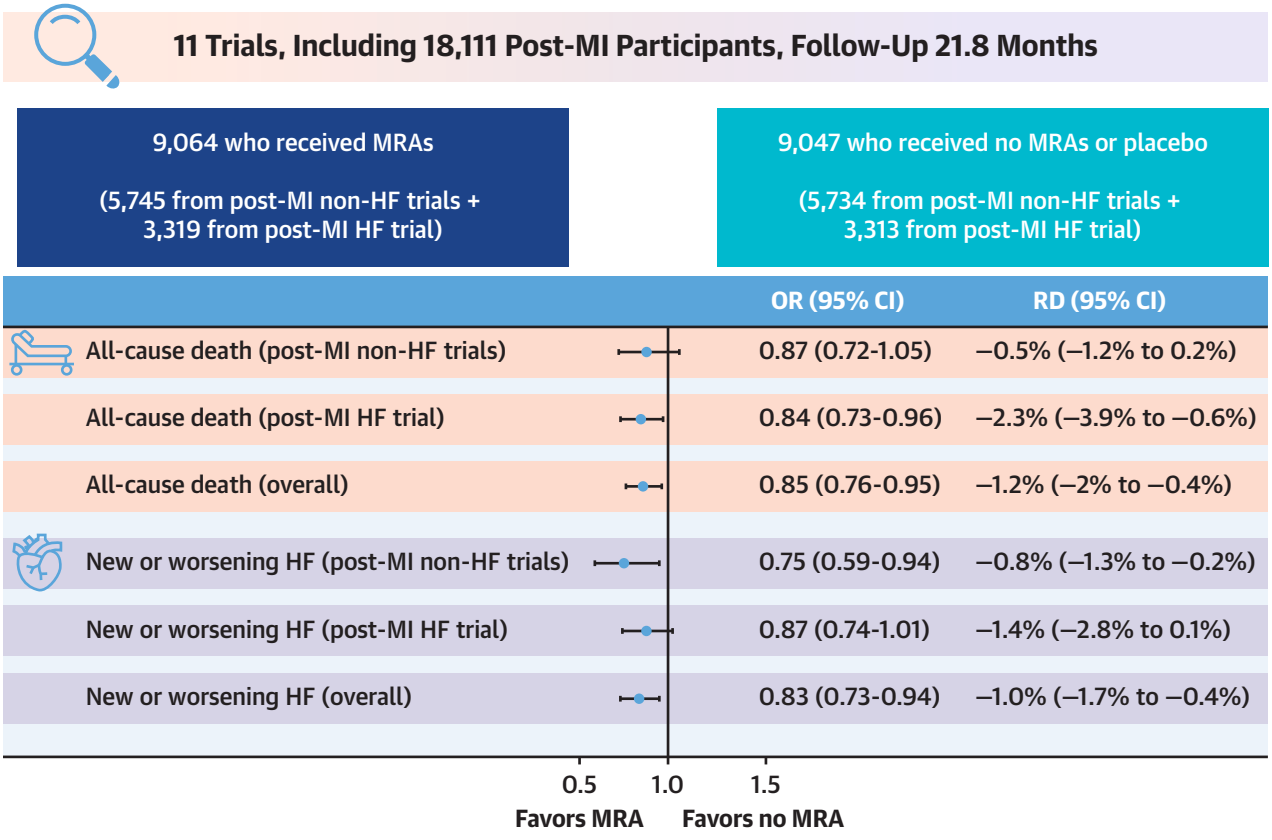
RESULTS

The PRISMA flowchart (**Figure 1**) describes the selection of studies. Given that the data were available after the published reports search date, the CLEAR trial data was manually added to the systematic review. Of the initial 582 records identified, 18 full-text studies were reviewed. After excluding 7 studies, 11 eligible trials involving 18,111 post-MI participants were included, of whom 9,064 participants were randomized to MRA and 9,047 were randomized to no MRA.[2-4,10-17] The **Central Illustration** provides an overview of the study's main findings.

TRIAL CHARACTERISTICS. **Table 1** summarizes the trial characteristics. The mean age ranged from 52 to 64 years, and female sex ranged from 14.3% to 70% in the included trials. Follow-ups ranged from 3 months to 36 months, with a weighted average of means of 21.8 months.

The trial by Pitt et al[2] (2003) (n = 6642) included post-MI participants with reduced ejection fraction of whom >90% had HF (post-MI HF trial). The other trials (Modena et al[10] [2001] [n = 46]; De Pasquale et al[11] [2005] [n = 687]; Uzuhasan et al[12] [2009] [n = 82]; Weir et al[13] [2009] [n = 100]; Kayrak et al[14]

CENTRAL ILLUSTRATION **Meta-Analysis of MRAs in MI Patients on All-Cause Death and New or Worsening Heart Failure**


11 Trials, Including 18,111 Post-MI Participants, Follow-Up 21.8 Months
9,064 who received MRAs
(5,745 from post-MI non-HF trials + 3,319 from post-MI HF trial)
9,047 who received no MRAs or placebo
(5,734 from post-MI non-HF trials + 3,313 from post-MI HF trial)
OR (95% CI)
RD (95% CI)
All-cause death (post-MI non-HF trials)
0.87 (0.72-1.05)
−0.5% (−1.2% to 0.2%)
All-cause death (post-MI HF trial)
0.84 (0.73-0.96)
−2.3% (−3.9% to −0.6%)
All-cause death (overall)
0.85 (0.76-0.95)
−1.2% (−2% to −0.4%)
New or worsening HF (post-MI non-HF trials)
0.75 (0.59-0.94)
−0.8% (−1.3% to −0.2%)
New or worsening HF (post-MI HF trial)
0.87 (0.74-1.01)
−1.4% (−2.8% to 0.1%)
New or worsening HF (overall)
0.83 (0.73-0.94)
−1.0% (−1.7% to −0.4%)
0.5
1.0
1.5
Favors MRA
Favors no MRA

d'Entremont M-A, et al. JACC Heart Fail. 2025;13(9):102531.

HF = heart failure; MRA = mineralocorticoid receptor antagonist; MI = myocardial infarction; RD = risk difference.

[2010] [n = 158]; Wu et al[15] [2013] [n = 616]; Montalescot et al[3] [2014] [n = 1,012]; Beygui et al[4] [2016] [n = 1,603]; Bulluck et al[16] [2019] [n = 113]; and Jolly et al[18] [2024] [n = 7,062]) included a majority of patients with no HF (post-MI non-HF trials).[2-4,10-16,18] Most trials were placebo-controlled except for Kayrak et al[14] [2010], Wu et al[15] [2013], and Beygui et al[4] [2016] who had usual care as the comparator.[3,14,15] The active treatment was oral spironolactone in 6 trials,[4,12,14-16,18] with 2 trials also using a loading dose of intravenous canrenoate before oral spironolactone,[4,16] oral eplerenone in 3 trials,[2,3,13] intravenous then oral canrenoate in 1 trial,[11] and oral canrenoate in 1 trial.[10] Each trial's definition of hyperkalemia or new or worsening renal failure are presented in Supplemental Table 2.

RISK OF BIAS. We summarized the risk of bias in Supplemental Table 3 for the primary outcome. Modena et al[10] (2001) was judged to have "some concern" given unclear trial procedures regarding blinding. Di Pasquale et al[11] (2005) was also considered to have "some concern" given the significant proportion of loss to follow-up. Finally, Kayrak et al[14] (2010), Wu et al[15] (2013), and Beygui et al[4] (2016) were judged to have "some concern" given the absence of a placebo in the comparator arm. We judged the other trials as having a low risk of bias.

There was no evidence of small study effects on visual inspection of the funnel plot for all-cause mortality with an Egger test value of $P = 0.82$ (Supplemental Figure 1).

OUTCOMES. Participants randomized to MRA had an OR of 0.85 for all-cause mortality compared to those randomized to no MRA (697/9,094 [7.7%] vs 803/9,047 [8.9%]; 95% CI: 0.76-0.95; $P = 0.003$; risk difference [RD] −1.2% [95% CI: −2.0% to −0.4%];

NNT: 67; I^2 = 0%; P = 0.50; 11 studies) (**Figure 2**, Supplemental Table 4).[2-4,10-16,18] Similarly, participants allocated to MRAs had an OR of 0.84 for cardiovascular mortality compared to participants without MRAs (557/8,555 [6.5%] vs 647/8,541 [7.6%]; 95% CI: 0.75-0.95; P = 0.006; RD: −1.1% [95% CI: −1.8% to −0.4%]; NNT: 91; I^2 = 16.9%; P = 0.31; 6 studies) (**Figure 3**).[2-4,11,13,18]

For the outcome of new or worsening HF, participants randomized to MRAs had an OR of 0.83 compared to patients without MRAs (471/8,570 [5.5%] vs 558/8,554 [6.5%]; 95% CI: 0.73-0.94; P = 0.004; RD: −1.0% [95% CI: −1.7% to −0.4%]; NNT: 100; I^2 = 26.8%; P = 0.22; 7 studies) (**Figure 4**).[2-4,10-12,18] For the other outcomes, participants receiving MRAs had an OR of 0.99 for recurrent MI (367/8,579 [4.3%] vs 370/8,563 [4.3%]; 95% CI: 0.85-1.15; P = 0.89; RD: 0.0% [95% CI: −0.6 to 0.6]; NNT: undefined; I^2 = 0%; P = 0.68; 7 studies)[2-4,10,11,13,18] (**Figure 5**), and an OR of 0.91 for life-threatening ventricular arrhythmias (124/8,255 [1.5%] vs 136/8,236 [1.7%]; 95% CI: 0.71-1.16; P = 0.44; RD: −0.1% [95% CI: −0.5% to 0.3%]; NNT: 1,000; I^2 = 18.6%; P = 0.29; 6 studies) (**Figure 6**).[2-4,12,13,18]

Regarding both safety outcomes, MRA-treated participants had an OR of 1.75 for hyperkalemia (296/8,568 [3.4%] vs 170/8,543 [2.0%]; 95% CI: 1.45-2.11; P < 0.001; RD: 1.4% [95% CI: 0.9%-2.1%]; NNH: 71; I^2 = 61.7%; P = 0.016; 7 studies[2-4,10,11,13,18]) (Supplemental Figure 2) and an OR of 1.12 for new or worsening renal failure as defined by the included studies (57/4,384 [1.3%] vs 51/4,377 [1.2%]; 95% CI: 0.77-1.64; P = 0.56; RD: 0.1% [95% CI: -0.3% to 0.7%]; NNH: 1,000; I^2 = 79.8%; P = 0.007; 3 studies[3,11,18]) (Supplemental Figure 3).

SUBGROUP AND SENSITIVITY ANALYSES. The effect of MRA was consistent in the post-MI trials with and without patients with HF, including all-cause mortality and new or worsening HF without evidence of subgroup interaction. The baseline risks for all-cause mortality in the post-MI HF trial and post-MI non-HF trials were 16.7% and 4.3%, respectively, with an RD of −2.3% (95% CI: −3.9% to −0.6%; NNT: 43) and −0.5% (95% CI: −1.2% to 0.2%; NNT: 200), respectively (Supplemental Tables 5 and 6). Likewise, the baseline risks for new or worsening HF in the post-MI HF trial and the post-MI non-HF trials were 11.8% and 3.19%, respectively, with an RD of −1.4% (95% CI: −2.8% to 0.1%; NNT: 71) and −0.8% (95% CI: −1.3% to −0.2%; NNT: 125), respectively.

The random effects analyses were consistent with the Peto OR analysis, with wider 95% CIs as between-trial heterogeneity increased (Supplemental Figures 4 to 10). Lastly, the sensitivity analysis, including only placebo-controlled trials for all-cause mortality and new or worsening HF was also consistent with the analyses including all trials (Supplemental Figures 11 and 12). Meta-regression analysis for all-cause mortality by follow-up duration (P = 0.26), PCI rates (P = 0.36), or baseline risk (P = 0.59) and for new or worsening heart failure by follow-up duration (P = 0.40), PCI rates (P = 0.88), or baseline risk (P = 0.91) did not demonstrate significant interaction.

DISCUSSION

KEY FINDINGS. In this study-level meta-analysis combining evidence from 11 randomized trials and a total of 18,111 participants, we found that MRAs provide a 15% decrease in the odds (1.2% absolute risk reduction) of all-cause mortality and a 17% decrease in the odds (1.0% absolute risk reduction) for new or worsening HF in post-MI participants. Although the effect was consistent between the post-MI HF trial and the post-MI non-HF trials, the absolute risk reductions were numerically smaller in the non-HF trials, given the lower baseline risks. However, the use of MRAs was associated with a 2-fold increase in the odds of hyperkalemia (1.5% absolute risk increase) without an increase in renal failure.

COMPARISON TO PRIOR EVIDENCE. The EPHESUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators) trial from Pitt et al[2] (2003) was the landmark trial that established the superiority of eplerenone over placebo in post-MI patients with left ventricular dysfunction ≤40% and HF. The REMINDER (Early Eplerenone Treatment in Patients With Acute ST-elevation Myocardial Infarction Without Heart Failure) and the ALBATROSS (Early Aldosterone Blockade in Acute Myocardial Infarction) trials both provided hypothesis-generating evidence regarding MRA use in post-MI patients, notably patients with ST-segment elevation myocardial infarction (STEMI), without HF.[3,4] The CLEAR trial did not demonstrate the benefit of spironolactone for both its co-primary outcomes of: 1) cardiovascular death or new or worsening HF; and 2) cardiovascular death, MI, stroke, new or worsening HF, but it did demonstrate a reduction in HF as compared to placebo.[18] EPHESUS participants had a baseline risk of 16.7% and 11.8% for death and new or worsening HF, respectively, at a mean follow-up of 16 months. On the other hand, CLEAR participants had a much lower baseline risk, with only 5.0% and

TABLE 1 Key Trial Characteristics

First Author, Year	Patients Randomized	Mean Age, y	Female, %	Study Population	Active Treatment	Comparator
Modena et al,[10] 2001	46	60	26.1	First episode of anterior MI	Potassium canrenoate 50 mg by mouth once daily	Placebo
Pitt et al,[2] 2003	6,632	64	28.9	Acute MI with LVEF <40% with HF or diabetes mellitus	Eplerenone 25-50 mg by mouth daily	Placebo
Di Pasquale et al,[11] 2005	687	63	29.4	First episode of STEMI, Killip class 1 or 2, with serum potassium level <5.0 mEq/L	Canrenoate intravenous during first 72 h, then canrenoate by mouth	Placebo
Uzunhasan et al,[12] 2009	82	52	70.0	First episode of STEMI without cardiogenic shock	Spironolactone 50 mg daily	Placebo
Weir et al,[13] 2009	100	59	23	Acute MI with an LVEF <40% without HF	Eplerenone 25-50 mg by mouth daily	Placebo
Kayrak et al,[14] 2010	158	56	78.2	First anterior STEMI with LVEF ≥40% and Killip class 1-2	Spironolactone 25 mg by mouth daily	Usual care
Wu et al,[15] 2013	616	59	27.1	First STEMI	Spironolactone 20 mg daily	Usual care
Montalescot et al,[3] 2014	1,012	58.6	18.7	STEMI without HF	Epleronone 25-50 mg by mouth daily	Placebo
Beygui et al,[4] 2016	1,603	58	17.0	STEMI and high risk NSTEMI	Canrenoate 200 mg intravenously, then spironolactone 25 mg daily	Usual care
Bulluck et al,[16] 2019	113	61	14.3	First STEMI without cardiogenic shock	Potassium canrenoate 200 mg intravenously, then spironolactone 25-50 mg	Placebo
Jolly et al,[18] 2024	7,062	61	20.3	STEMI or high-risk NSTEMI	Spironolactone 25 mg daily	Placebo

BNP = B-type natriuretic peptide; CV = cardiovascular; HF = heart failure; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NR = not reported; NSTEMI = non-ST-elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-elevation myocardial infarction.

2.4% experiencing death and new or worsening HF, respectively, at a median follow-up of 3 years. This difference in baseline risk suggests that post-MI patients with HF have a worse prognosis as compared to patients without HF, although secular trends in cardiovascular interventions should be considered. Given that both sacubitril-valsartan and sodium-glucose cotransporter 2 have not shown significant benefits in post-MI patients, differential patterns of revascularization and improvements in critical care cardiology likely played a role in explaining the baseline risks.[19-21] Whereas 100% of CLEAR participants received PCI, only 45% of EPHESUS participants received reperfusion therapy or revascularization (23.8% received PCI). Although our meta-regression analysis by PCI rates and baseline risk did not show significant interaction, it was most likely severely underpowered. It should be interpreted cautiously and not modify the results' interpretation.

When the evidence from post-MI non-HF trials is combined with the CLEAR results, the effect estimates for death and new or worsening HF on the relative risk scale are similar to the EPHESUS trial results.[2,18] However, post-MI HF patients seem to benefit more from MRA therapy than their non-HF counterparts when considering the absolute risk reductions.

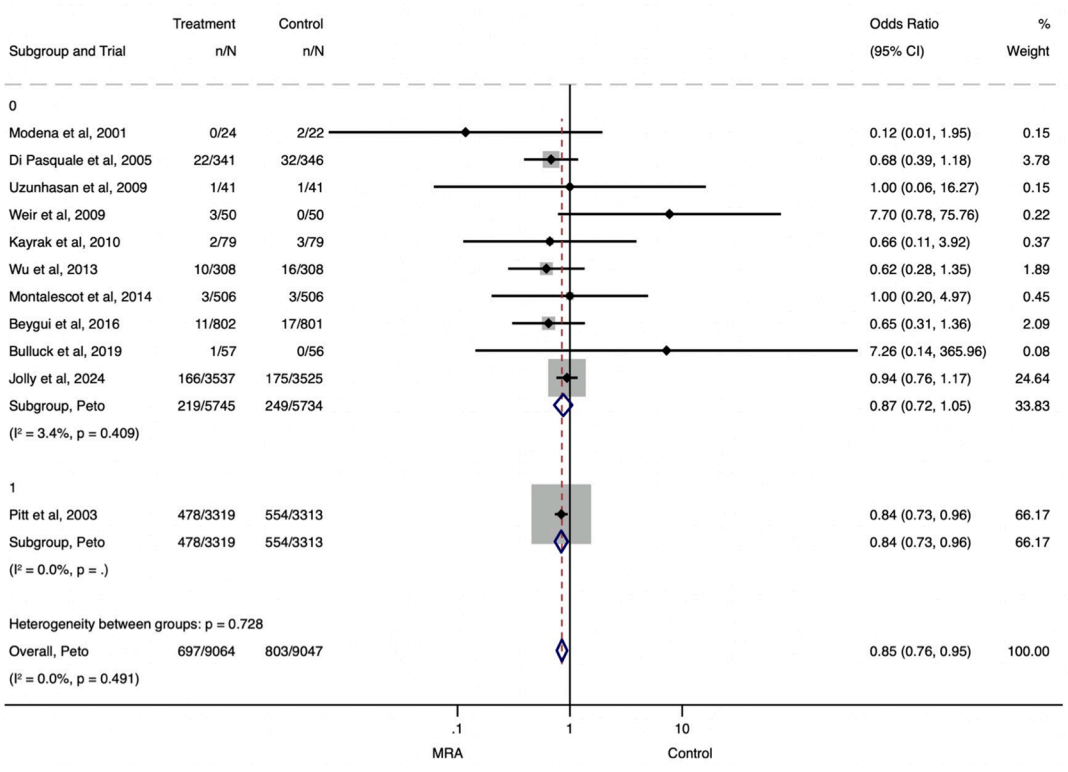
IMPLICATIONS FOR CLINICAL PRACTICE AND FUTURE RESEARCH. Despite obtaining a class 1 indication on a background of level A evidence in the European Society of Cardiology acute coronary syndrome guidelines, MRAs post-MI patients with left ventricular dysfunction <40% and HF or diabetes post-MI are underprescribed.[1] In a contemporary STEMI cohort, only 1 in 4 MRA-eligible patients were prescribed an MRA within 3 months following hospitalization.[22] Given the gap in evidence before the CLEAR trial, no recommendations have been made regarding MRA use in a more unselected post-MI population. Our meta-analysis suggests mortality and HF benefit with no interaction when considering the EPHESUS trial compared to other post-MI trials not specifically recruiting HF patients. However, given the smaller absolute risk reduction in the post-MI non-HF trials, shared decision-making between clinicians and patients is essential in balancing the benefits and potential harms should MRAs be considered in this population.

Finerenone, a selective nonsteroidal MRA, has emerged as a new promising HF therapy. The FINEARTS-HF (Finerenone in Heart Failure with Mildly Reduced or Preserved Ejection Fraction) trial randomized 6,001 patients with HF and a left ventricular ejection fraction ≥40% to finerenone vs placebo.[23] Participants allocated to finerenone

TABLE 1 Continued

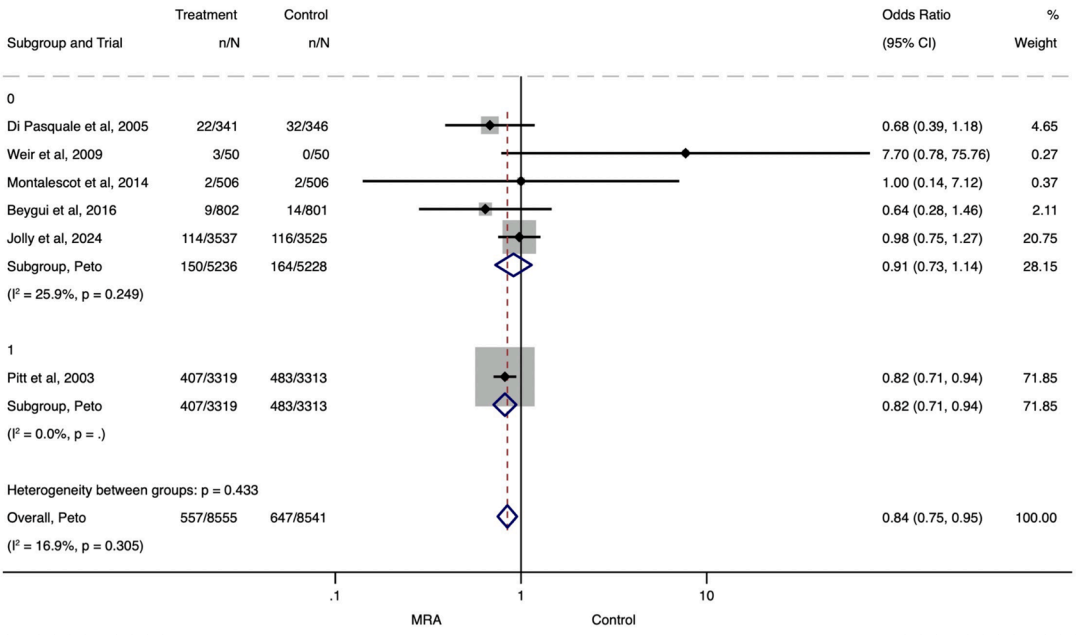
LVEF at Baseline, %	Killip Class Description	HF at Presentation, %	PCI Rates, %	Key Outcomes	Follow-Up, mo
46.5	1 = 73.9%	26.1	0	Echocardiography parameters N-terminal propeptide of type III collagen measurements at 12 mo	12
33	≥2 = 90%	90	23.8	All-cause mortality CV death, HF, acute MI, stroke or ventricular arrhythmia	16 (mean)
44.6	≤2 = 100%	Unavailable	33.5	Echocardiographic parameters	6
45.5	1 = 80.5% 2 = 19.5%	19.5	Unavailable	Echocardiographic parameters	6
33.8	1 = 100%	0	74	Echocardiographic parameters Plasma concentrations of matrix metalloproteinases 2 and 9	6
50	≤2 = 100%	Unavailable	100	Echocardiographic parameters	6
NR	1 = 98.7%	1.3	40.7	Echocardiographic parameters	12
NR	1 = 100%	0	86.1	Primary composite outcome of CV death, new or worsening HF, ventricular arrythmia, LVEF <40% or elevated BNP at 1 mo	10.5 (mean)
50	1 = 92.5%	7.5	90.3	Primary composite outcome of death, resuscitated cardiac arrest, ventricular arrythmia, indication for ICD, new or worsening HF	6
47	NR	3.5	100	MI size on cardiac magnetic resonance	3
NR	1 = 99.3%	0.7	100	Co-primary of: 1) CV death or new or worsening HF; and 2) CV death, MI, stroke, or new or worsening HF	36 (mean and median)

FIGURE 2 Post-MI HF vs Non-HF Trials for All-Cause Mortality (Peto OR)



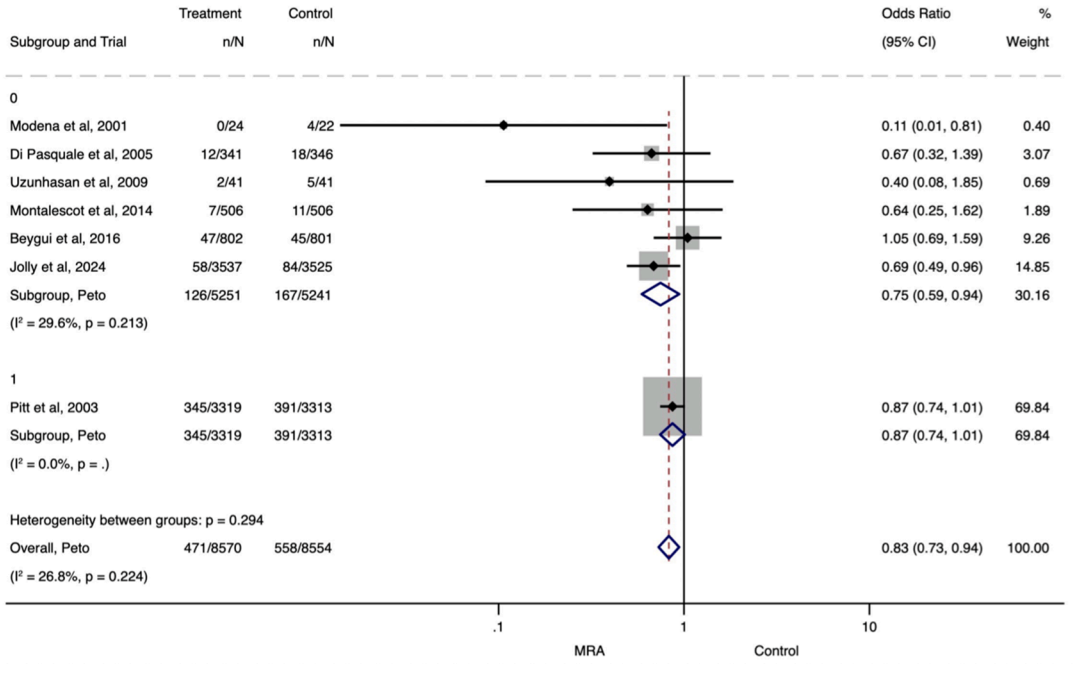
Where 0 indicates post-MI HF trial and 1 indicates post-MI non-HF trials.[2-4,10-16,18] HF = heart failure; MI = myocardial infarction; OR = odds ratio; other abbreviation as in Figure 1.

FIGURE 3 Post-MI HF vs Non-HF Trials for Cardiovascular Mortality (Peto OR)



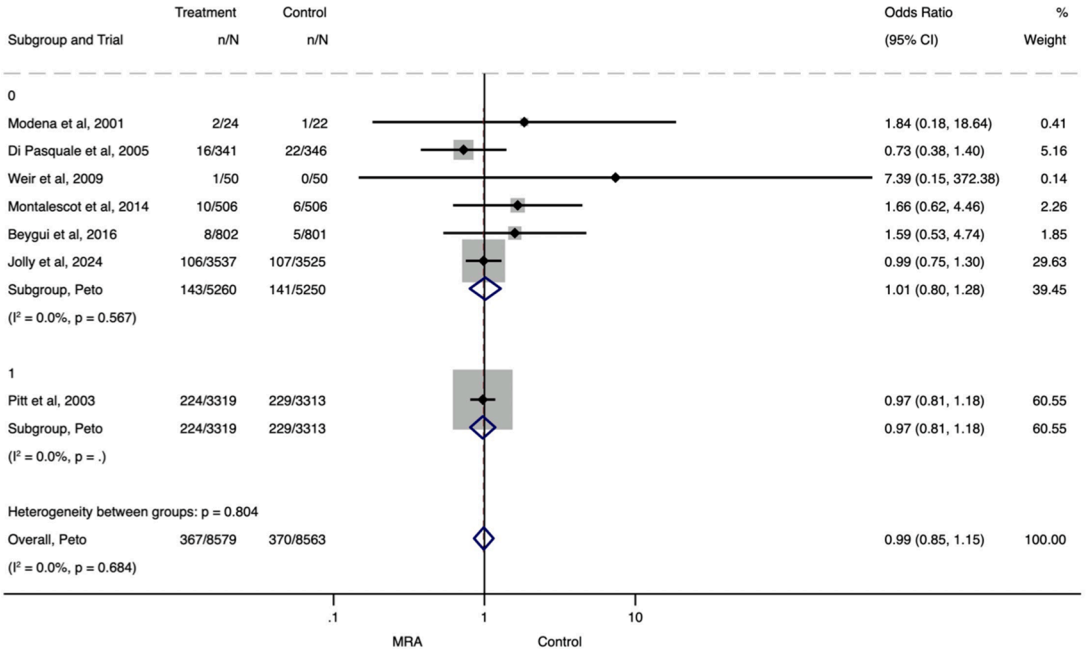
Where 0 indicates post-MI HF trial and 1 indicates post-MI non-HF trials.[2-4,11,13,18] Abbreviations as in Figures 1 and 2.

FIGURE 4 Post-MI HF vs Non-HF Trials for New or Worsening HF (Peto OR)



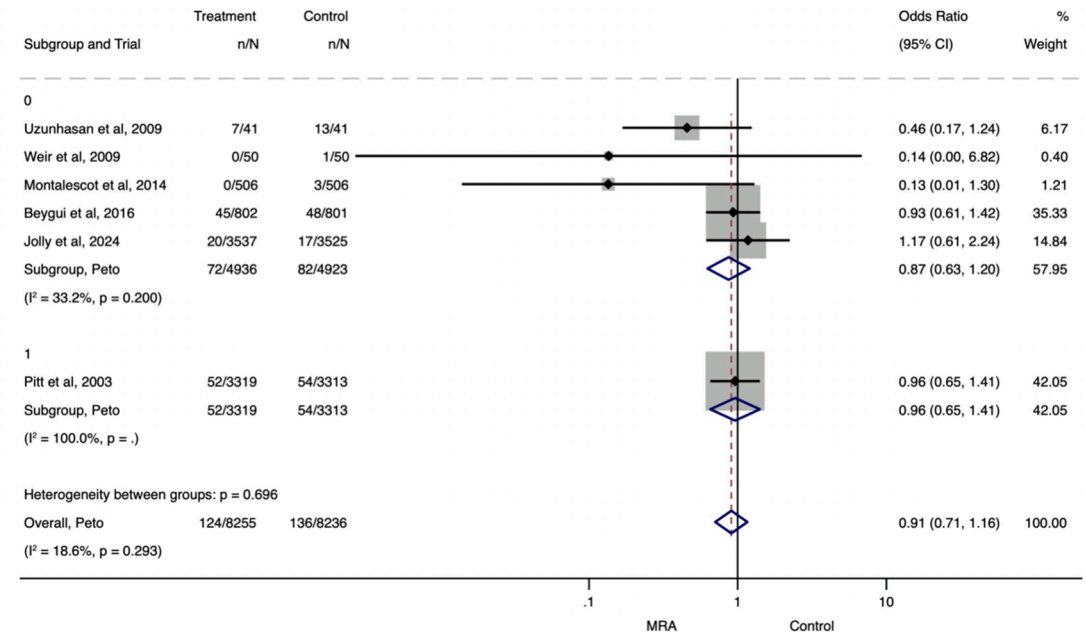
Where 0 indicates post-MI HF trial and 1 indicates post-MI non-HF trials.[2-4,10-12,18] Abbreviations as in Figures 1 and 2.

FIGURE 5 Post-MI HF vs Non-HF Trials for Recurrent MI (Peto OR)



Where 0 indicates post-MI HF trial and 1 indicates post-MI non-HF trials.[2-4,10,11,13,18] Abbreviations as in Figures 1 and 2.

FIGURE 6 Post-MI HF vs Non-HF Trials for Life-Threatening Ventricular Arrhythmias (Peto OR)



Where 0 indicates post-MI HF trial and 1 indicates post-MI non-HF trials.[2-4,12,13,18] Abbreviations as in Figures 1 and 2.

experienced a 16% relative risk reduction for the composite of total HF events or cardiovascular death at a median follow-up of 32 months (rate ratio: 0.84 [95% CI: 0.74-0.95]; $P = 0.007$).[23] Whether these promising results translate into benefits for post-MI patients without HF warrants further investigation with large randomized controlled trials.

STUDY LIMITATIONS. First, we did not analyze individual participant-level data. Therefore, our capacity to assess efficacy and safety outcomes with greater granularity and to perform patient-level analyses is limited. Second, although study-level HF status was available for most trials, the exact proportions of Killip 1 and 2 patients in the Di Pasquale et al[11] (2005) and Kayrak et al[14] (2010) trials were unavailable. Although informative, these data would not have changed our analytic approach and interpretation of the results, given the small number of patients in these trials. Third, we also acknowledge the wide range of follow-up times, such as 3 months for the Bulluck et al[16] trial and 36 months for the Jolly et al[18] trial. Fourth, the results must be interpreted knowing that 3 different types of MRA were used, and with canrenoate being used both in its intravenous and oral formulations. Differences in pharmacokinetics or pharmacodynamics may have played a role in modulating between trial differences, although statistical heterogeneity for the primary and secondary efficacy outcomes were low. Finally, differences in outcome definition between trials, notably for hyperkalemia and new or worsening renal failure, may have introduced some variability and likely explain some of the heterogeneity, although this unlikely impacted our overall findings.

CONCLUSIONS

In post-MI patients, the totality of the evidence suggests that MRA therapy results in a reduction of both death and new or worsening HF. Given the lower absolute risk in post-MI non-HF patients, an individualized approach based on baseline risk should be considered.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: This meta-analysis shows that post-MI mineralocorticoid blockade results in a reduction in all-cause mortality and new or worsening HF but an increase in hyperkalemia. Although mineralocorticoid antagonists remain a cornerstone therapy in post-MI patients with <40% ejection fraction and HF, there is numerically less absolute benefit in post-MI patients without HF.

TRANSLATIONAL OUTLOOK: An individualized approach based on baseline risk should be considered when considering prescribing a mineralocorticoid antagonist in post-MI patients without HF. Large randomized controlled trials with novel mineralocorticoid antagonists in this patient population are warranted.

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KEY WORDS heart failure, mineralocorticoid receptor antagonist, myocardial infarction

APPENDIX For supplemental tables and figures, please see the online version of this paper.